REMARKS

The Office Action has rejected claims 26, 27, 31 and 32 under two separate 35 U.S.C. §112 first paragraph. In light of the enclosed declaration and the arguments below, Applicants respectfully request reconsideration.

On Wednesday, April 1, inventor Professor Paul Ahlquist and Patent Attorney Jean Baker interviewed Examiner Chen telephonically. Applicants and their attorney thank Examiner Chen for the courtesy of his time and for his helpful suggestions.

At the interview, Applicants discussed both Section 112 rejections, described in more detail below. Applicants presented evidence that the existence and activity of delta9 fatty acid desaturases (usually called SCD genes) have been shown for many mammals, including mouse, rat, sheep, pig, cow, dog, chimpanzee and human. Applicants also discussed positive strand RNA viruses and whether a membrane modulated agent might be expected to affect the viruses when viewed as a generic group.

Examiner Chen and Applicants agreed that Applicants would submit a listing of the various literature references that Applicants discussed in the interview and would present further evidence on the question of BMV as a model for positive strand RNA viruses. Applicants have complied with both of these agreements below.

35 U.S.C. §112, First Paragraph Rejections

Claims 26 and 27 are rejected under 35 U.S.C. §112, first paragraph, on the ground that the claims fail to comply with the written description requirement. The Office Action comments that claims 26 and 27 read on using delta9 fatty acid desaturases enzyme "derived from various organisms." The Office Action notes that "a search of OLE1 gene in the art only results in the OLE1 gene of ...a dimorphic pathogenic fungus and ... yeast."

Applicants and their attorney discussed this rejection at great length with Examiner Chen. Applicants and their attorney pointed out that the existence and activity of delta9 fatty acid desaturases have been shown for many mammals at the time of the filing of the application. Applicants note that the following publications describe delta9 fatty acid desaturases (usually called SCD genes):

References:

Human:

* Li et al (1994) Int J Cancer 57:348-352 cloned a portion of the human SCD1 gene by homology to the rat gene and showed it to be expressed in various normal and tumor tissues.

* Dias and Parsons (1995) J Lipid Res 36:552-563 showed that, as universally expected, a human cell line expressed delta9 fatty acid desaturase activity assayable in vitro.

* On 6 June 1997, Craft et al. submitted to GenBank the sequence of an ~1.5 kb cDNA containing the complete SCD coding region and flanking sequences, and showing the strong homology of human SCD to rat, etc. (GenBank accession no. Y13647.)

* Zhang et al. (1999) Biochem J 340:255-264 cloned the human SCD1 genomic DNA and characterized its expression.

Other mammalian SCDs

* St John et al (1991) J Animal Sci 69:1064-1073 showed the presence of SCD activity in bovine tissue.

* Ward et al (1997) Biochem Soc Trans 25:s673 cloned the sheep (ovine) SCD gene.

* On 29 Mar 1999 Hamasima entered the sequence of a pig SCD cDNA into GenBank (GenBank accession no. AU055693).

* Chung et al. (2000) Biosci Biotech Biochem 64:1526-1530 cloned bovine SCD cDNA, characterized its expression, and showed the strong aa similarity (88 - 96.5%) of bovine SCD with mouse, rat, sheep, pig and human SCDs.

* Gene Cards (www.genecards.org) shows entries for chimpanzee and dog SCD genes, noting them to be 99 and 89% similar to human SCD.

* Stukey et al. (1990) The Journal of Biochemistry, Vol. 265, No. 33, pp. 20144-20149, "The OLE1 Gene of Saccharomyces cerevisiae Encodes by the Δ9 Fatty Acid Desaturase Gene."

Applicants believe that this listing and discussion of various delta9 fatty acid desaturases is sufficient to address the Examiner's concerns.

The Office Action noted that "there is no evidence of record that shows whether they have the same function as the used delta9 fatty acid desaturases other that the rat stearoyl CoA desaturase." As noted in prior communications and above, delta9 fatty acid desaturases activity has been shown for at least mouse, rat, cow, human SCDs. Applicants made the point to Examiner Chen that the sequence identity between yeast and rat OLE1/SCD and mouse and yeast OLE1/SCD are low - specifically on the order of 35-36%. In contrast, the sequence identity among mammalian SCDs is approximately 88-99%.

In prior communications, Applicants have noted that rodent delta9 fatty acid desaturases were already known to efficiently function in yeast as replacement for the normally essential yeast OLE1 gene (Stukey et al., 1990). Accordingly, the ability of the relatively divergent mouse and rat SCDs to function in the place of yeast OLE1 gene makes it extremely probable that other mammalian SCD genes would similarly substitute. During the telephonic interview, Professor Paul Ahlquist made the point that the sequence divergence between the yeast and rat sequences are much greater than the sequence divergence among various mammalian genes.

Applicants believe that they have fully and carefully addressed the Examiner's concerns about claim coverage of yeast and mammalian delta9 fatty acid desaturase species.

Claims 26 , 27, 31 are rejected and 32 under 35 U.S.C. §112, first paragraph, on the ground that the specification, while being enabling for evaluating a substance as brome mosaic virus (BMV) RNA antiviral agent by using yeast delta9 fatty acid desaturase, does not reasonably provide enablement for evaluating a substance as positive strand RNA antiviral agent by using a yeast OLE1 desaturase or mammalian delta9 fatty acid desaturase.

During the interview, Examiner Chen challenged Applicants to address whether it could be shown that a membrane modulating agent might affect positive strand RNA viruses as a group. The Examiner asked Applicants to clarify points regarding

unsaturated fatty acids as key determinants of membrane fluidity and the crucial nature of membranes to the replication of positive strand RNA viruses.

Applicants have enclosed a Declaration of Professor Paul Ahlquist addressing Examiner Chen's question. Note that Professor Ahlquist makes the following points:

- (Declaration Paragraph 2) Unsaturated fatty acids are key determinants of membrane fluidity and all studied eukaryotes use delta9 fatty acid desaturases to carry out the first step of synthesizing unsaturated fatty acids.
- (Declaration Paragraph 3) Membranes are crucial to the replication of positive strand RNA viruses, and all positive strand RNA viruses assemble the machinery for genomic RNA replication on one or more intracellular lipid bilayer membrane. In the Declaration, Professor Ahlquist supplies documentation and citations to this point.
- (Declaration Paragraph 4) Professor Ahlquist discussed experiments with different positive strand RNA viruses demonstrating that various membrane-associated replication structures share common features that are the crucial for supporting RNA replication.

Applicants assert that the telephonic interview with Examiner Chen, the above discussion and the enclosed Declaration combined to adequately address the issue of whether membrane modulating agents would affect positive strand RNA viruses.

Examiner Chen and Applicants discussed BMV as a model system and Examiner Chen requested that Applicants address BMV as a model system for membrane associated replication structures. In paragraph 5 of his declaration, Professor Ahlquist addresses this point. Note that paragraph 5 cites references to the use of BMV as a model system and notes that the Ahlquist lab has used BMV in many demonstrations of the RNA replication complex associated with membranes. Paragraph 6 of the Declaration shows support for the use of BMV as a model system for membrane-associated replication factors by describing frequent citation of results derived with BMV in many academic papers on positive strand RNA viruses and include the adoption of Ahlquist lab results on BMV as the major current model for RNA replication complex formation by hepatitis C virus, one of the most clinically important human positive strand RNA viruses.

Summary

Applicants have amended the claims in this application or provided arguments to respond to all of the Examiner's rejections. Accordingly, Applicants respectfully request the Examiner to reconsider said rejections and to issue a Notice of Allowance in the claims currently under consideration.

Fees

A petition for a 1 month extension of time accompanies this response so that the response is timely filed. No other extension of time is believed due, but should any additional extension be due, in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the extension fee to Deposit Account No. 17-0055. No additional fees are believed due; however, if any fees are due, in this or any subsequent response, please charge Deposit Account 17-0055.

Respectfully submitted,

Date: April 20, 2009

By: _____

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